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ORIGINAL ARTICLE

Non-invasive assessment of coronary artery disease with CT coronary angiography and SPECT: a novel dose-saving fast-track algorithm

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Abstract
Purpose To validate a new low-dose and rapid stepwise individualized algorithm for non-invasive assessment of ischemic coronary artery disease by sequential use of prospectively ECG-triggered low-dose CT coronary angiography (CTCA) and low-dose single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI).
Methods Forty patients referred for elective invasive coronary angiography (CA) were prospectively enrolled to undergo a comprehensive non-invasive evaluation with low-dose CTCA and a dose-reduced stress/rest SPECT-MPI scan (using dedicated reconstruction algorithms for low count scans). The following algorithm was reviewed: CTCA first, followed by a stress-only MPI if a coronary stenosis (≥ 50% diameter narrowing) or equivocal findings were observed. Only abnormal stress MPI scans were followed by rest MPI. The accuracy of the individualized algorithm to predict coronary revascularization and its mean effective radiation dose were assessed.
Results CTCA documented CAD in 18 and equivocal findings in two patients, thus, requiring additional stress MPI scans. Of these, 16 were abnormal, therefore requiring a rest MPI scan, revealing ischemia in 15 patients. Sensitivity, specificity, negative and positive predictive value, and accuracy of the individualized algorithm for predicting coronary revascularization was 93.3%, 96.0%, 96.0%, 93.3% and 95.0% on a per-patient base. The mean effective radiation dose was significantly lower for the individualized (4.8±3.4 mSv) versus the comprehensive method (8.1±1.5 mSv) resulting in a total population radiation dose reduction of 132.6 mSv.
Conclusion This new individualized low-dose algorithm allows rapid and accurate prediction of invasive CA findings and of treatment decision with minimized radiation dose.

Keywords CT coronary angiography · Prospective ECG-triggering · Coronary artery disease · Single-photon emission computed tomography

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Introduction

In Western countries, coronary artery disease (CAD) is one of the major causes for morbidity and mortality. So far, invasive coronary angiography (CA) is the standard of reference for detection of CAD, although it is costly and associated with a non-negligible rate of procedural morbidity and mortality [1, 2]. Therefore, great efforts have been made to develop new non-invasive approaches for imaging coronary atherosclerosis. A widely used and well-established diagnostic tool for detecting ischemia is myocardial perfusion imaging (MPI) with single photon emission computed tomography (SPECT)

[3]. However, it does not offer anatomic information for targeting revascularization. A recently introduced non-invasive imaging method is computed tomography coronary angiography (CTCA) [4], which permits visualization of the coronary arteries and stenoses. Since 1999, when the first multislice spiral computed tomography was made available [5], this method has been developed continuously [4]. CTCA has a high negative predictive value (NPV) but does not provide functional information on lesion severity as reflected by its modest positive predictive value (PPV) [6, 7], which has affected its role in the clinical management in daily routine. A combination of SPECT-MPI with CTCA has therefore been suggested, as it would overcome the shortcomings of each technique and allow comprehensive anatomical and functional CAD assessment. Although feasibility [8, 9] and the potential added clinical value of non-invasive imaging combining MPI with CTCA has been documented [10], the practicability is so far hampered due to a total radiation burden up to 41 mSv [11] and long duration of the protocol.

Hence, there is an ongoing debate about the necessity and the correct indication of the combination of these two non-invasive diagnostic methods. Recent developments including prospective ECG-triggering allowing low-dose CTCA [12, 13] and improved reconstruction algorithms allowing tracer dose reduction for SPECT-MPI [14] represent important contributions which may shift the balance from harms towards benefits.

Using the latest technical refinements to ensure low effective radiation dose from CTCA (prospective triggering) and from SPECT-MPI (new reconstruction algorithm for low counts scanning) we aimed at evaluating the accuracy to assess CAD and the radiation dose of a sequential algorithm in which the result of each diagnostic step determined whether an additional test was necessary within the following sequence: CTCA, SPECT-MPI at stress, and SPECT-MPI at rest.

Materials and methods

Study population

Forty patients with low to intermediate pretest probability who were referred for elective invasive CA due to suspected CAD were prospectively enrolled to undergo a low-dose CTCA and a low-dose stress/rest SPECT-MPI scan on the same day. Exclusion criteria were: known CAD, hypersensitivity to iodinated contrast material, renal insufficiency (creatinine levels >150 μmol/l), non-sinus rhythm, or hemodynamic instability. Patients and invasive cardiologists in the catheterization laboratory were unaware of the CTCA and stress/rest SPECT-MPI results. The study protocol was approved by the institutional review board (local ethics committee of the University Hospital Zurich) and written informed consent was obtained from each patient.

Proposed algorithm

After completing all non-invasive CTCA and stress/rest MPI scans in each patient we reviewed an individualized algorithm using the following optimized stepwise approach: First, CTCA findings were analyzed. Second, stress-only SPECT-MPI was added if at least one coronary stenosis (≥ 50% diameter narrowing) or equivocal findings were observed by CTCA. Third, rest MPI was included into the analysis if stress MPI revealed abnormal findings. Accuracy of this individualized algorithm to predict decisions of the interventional cardiologists with regard to perform percutaneous coronary intervention (PCI) in the catheterization laboratory based on CA and clinical information was assessed. These decisions served as standard of reference.

CTCA data acquisition and analysis

CTCA scans were performed on a stand-alone LightSpeed VCT XT scanner (GE Healthcare) using prospective ECG-triggering as recently established [12] and validated [15]. By choosing the smallest possible window at only one distinct end-diastolic phase of the RR-cycle (i.e., 75%, with a padding of 0 ms) and by adapting the tube current and voltage to the body-mass index (BMI) [16] we ascertained the lowest achievable effective radiation dose delivery. If necessary, patients received intravenous metoprolol (5 to 20 mg) (Metoprolol, AstraZeneca, London, UK) to achieve a target heart rate <63 bpm. Any step artifact was categorized as non-diagnostic. Two readers experienced in cardiac radiology blinded for the SPECT-MPI results assessed all coronary vessels for the presence of significant stenosis, defined as narrowing of the coronary luminal diameter≥50%.

SPECT-MPI data acquisition and analysis

Adenosine stress and tracer injection was performed while the patient was lying on the scanner. Adenosine stress/rest SPECT-MPI was acquired immediately (i.e., <5 min) after tracer injection on a dual-head detector camera (Ventri, GE Healthcare, Milwaukee, USA) to shorten total protocol time, as recently established [17], without the standard 90 min delay between tracer application and SPECT-MPI acquisition. The SPECT-MPI imaging period was approximately 15 min for stress and rest each. As previously validated [14], a new dedicated iterative algorithm (Evolution for Cardiac, GE Healthcare), allowing a 50% tracer reduction by compensating for low count imaging was used for image

reconstruction on a Xeleris workstation (GE Healthcare). Accordingly, we used half of the recommended standard 99mTc-tetrofosmin activity adapted to the BMI for stress and rest (i.e., BMI<25 kg/m^2: stress 150 MBq, rest 450 MBq; BMI≥25 kg/m^2: stress 200 MBq, rest 600 MBq). An unenhanced CT scan was used for soft-tissue attenuation correction. Image analysis was performed using standard software according to clinical practice as previously reported [6, 7], blinded for the CTCA findings.

Effective radiation dose

Effective radiation dose for CTCA was estimated as dose-length product (DLP) times a conversion coefficient for the chest k. The commonly used conversion factor is $k = 0.014\ mSv/mGy \times cm$ [18]. However, we chose a higher factor, i.e., $k = 0.017\ mSv/mGy \times cm$ [19] to account for the higher susceptibility of females to breast cancer as we included 17 females in our study. Radiation dose for SPECT MPI was calculated as 99mTc-tetrofosmin activity times 7.9 mSv/GBq as suggested by the International Commission on Radiological Protection (ICRP) [20]. For invasive CA (diagnostic part only), dose-area product (DAP) was multiplied with a conversion factor for chest ($k = 0.22\ mSv/mGy \times cm$) according to the National Radiological Protection Board tables [21]. Total and mean effective radiation dose of the individualized algorithm for all patients was compared to the radiation dose if all tests would have been applied to all patients.

Invasive coronary angiography data acquisition and analysis

Experienced interventional cardiologists performed invasive CA in the catheterization laboratory. A coronary stenosis was defined as a diameter reduction of ≥50% by visual assessment. The decision towards percutaneous coronary intervention (PCI) was made by the interventional cardiologists during CA. This decision was based on an integration of anatomic coronary lesion findings with the previously assessed clinical information which had originally triggered the referral for invasive CA. The operators were blinded for the information obtained in the non-invasive part of the study (CTCA, SPECT-MPI).

Statistical analysis

Results from the individualized algorithm were compared to the decision made by the interventional cardiologist towards coronary revascularization per patient and per vessel territory. Sensitivity, specificity, PPV, NPV, and accuracy were calculated for the individualized algorithm to predict revascularization decision. *P*-values of the difference between the two mean effective radiation doses were calculated using a Wilcoxon signed ranks test. *P*-values of less than 0.05 were considered statistically significant. All *P*-values are two-sided. SPSS software (SPSS 15.0, SPSS Inc.) was used for statistical testing.

Results

Each examination, i.e., CTCA, SPECT-MPI and invasive CA was successfully performed in all 40 patients. Baseline characteristics of all patients included in this study are given in Table 1.

Algorithm

Figure 1 displays the individualized rapid low-dose algorithm. Twenty patients had no significant stenosis in CTCA (including nine with normal coronaries and 11 with non-obstructive coronary atherosclerosis) and therefore no further diagnostic test was needed. In two patients with equivocal findings, a stress SPECT-MPI was added, which was normal and, therefore, no rest MPI deemed necessary. Similarly, stress SPECT-MPI was added in 18 patients with at least one stenosis (in total there were 56 lesions) in CTCA, revealing an abnormal finding in 16 patients triggering the request for a rest SPECT-MPI. The latter documented total (n=9) or partial (n=6) reversibility of the defect in 15 patients, indicating ischemia. In one patient, the resting scan documented a fixed defect, reflecting a scar. Sensitivity, specificity, NPV, PPV, and accuracy of the individualized algorithm for predicting coronary revascularization was 93.3%, 96.0%, 96.0%, 93.3% and 95.0% per

Table 1 Baseline characteristics (n=40)

Mean age ± SD (years)	62±8.3
Male (n)	23
Mean body-mass index ± SD (kg/m^2)	27.1±5.1
CvRF	
Positive family history (%)	35
Smoking (%)	40
Diabetes (%)	13
Hypertension (%)	63
Dyslipidemia (%)	50
Typical chest pain (%)	50
Atypical chest pain (%)	45
Dyspnea (%)	20

SD Standard deviation, *CvRF* Cardiovascular risk factors

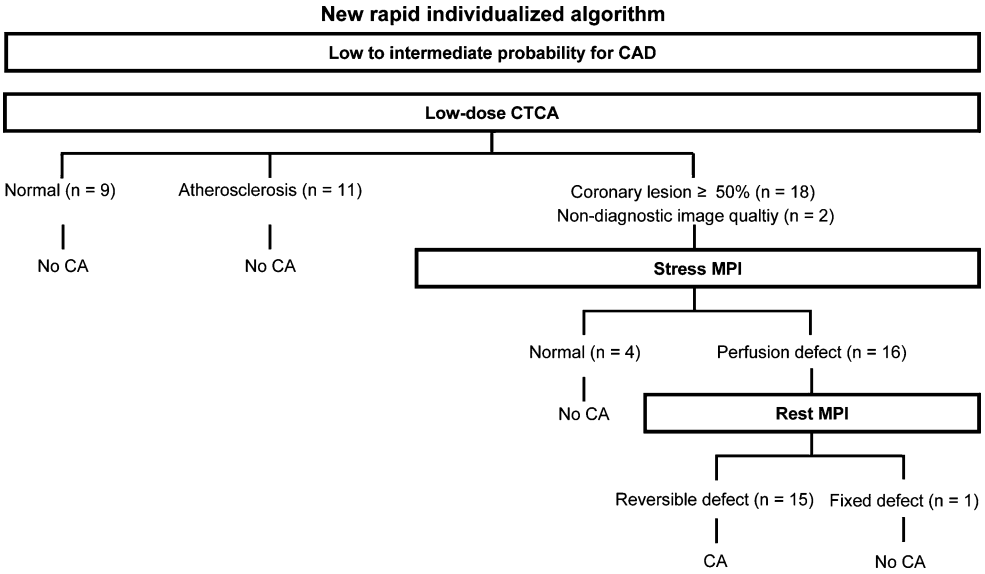

Fig. 1 Individualized low-dose algorithm showing decisions made in the study population (*CA* invasive coronary angiography, *CAD* coronary artery disease, *CTCA* computed tomography coronary angiography, *MPI* myocardial perfusion imaging)

patient and 90.0%, 95.0%, 97.9%, 78.3% and 94.0% per vessel territory.

Invasive coronary angiography

Interventional cardiologists decided to perform a PCI in 21 coronary lesions of 15 patients.

Effective radiation dose

The mean effective radiation dose from the non-invasive imaging study was 8.1±1.5 mSv per patient if all three steps of the diagnostic algorithm were applied, adding up to 325.7 mSv total effective radiation dose applied to the entire study population (Fig. 2). By using the individualized algorithm the mean effective radiation dose was significantly lower (4.8±3.4 mSv) as less than half of the patients needed all diagnostic steps. This reduced the total effective radiation dose deployed to the patient population by 132.6 mSv to 193.1 mSv ($p<0.001$). The mean effective radiation dose from CTCA, which would be performed in all 40 patients, was 2.1 ± 0.7 mSv(DLP 120.8 ± 43.2 mGycm). Radiation from stress-only SPECT-MPI, which would be required in 20 patients, was 1.4±0.2 mSv resulting from 99mTc-tetrofosmin activity (207.6±33.7 MBq) and 1.1±0.1 mSv from the unenhanced CT for attenuation correction (DLP 62.6±6.1 mGycm), adding up to 2.5±0.2 mSv. Rest SPECT-MPI, requested in 16 patients, resulted in a mean radiation dose of 3.9 ± 0.5 mSv(557.2 ± 74.7MBq).

Mean effective radiation dose from purely diagnostic invasive CA (8.7±4.2 mSv; DAP 39.5±19.1 mGycm^2) was comparable to the unselective combination of CTCA with stress/rest SPECT-MPI, but significantly higher than the mean effective radiation obtained from the individualized algorithm ($p<0.001$).

Discussion

Our results document that the proposed individualized rapid algorithm for assessing CAD in patients with low to intermediate pretest likelihood has an excellent ability to either rule out functionally relevant stenoses or to predict the necessity of revascularization procedure despite minimized radiation dose exposure. This is remarkable as both non-invasive components, i.e., CTCA and SPECT-MPI, were performed with latest techniques allowing for massive reduction in total effective radiation dose. Prospective ECG-triggering has allowed to substantially reduce radiation dose of CTCA from about 15 to 20 mSv down to 1 to 3 mSv at maintained image quality [12] and accuracy [15, 22]. The estimated radiation dose from CTCA in the present study (2.1±0.7 mSv) lies well within this previously reported range. Similarly, we have minimized the radiation dose from SPECT-MPI by using a dedicated iterative reconstruction algorithm allowing to inject half of the standard isotope activity. Another strength of the present algorithm lies in the fact that following the stepwise approach has prevented many patients from undergoing the whole sequence of the non-invasive tests, which resulted in a further significant decrease in radiation burden of the entire study population.

Several studies have documented the complementary information provided by the two non-invasive diagnostic methods CTCA and SPECT MPI [6, 22, 23]. We suggest an algorithm starting with CTCA first. In our study, 50% of all patients could be excluded correctly after CTCA from further tests. This reflects the high NPV of 64-slice CTCA, which was demonstrated in earlier studies [6, 15]. The ability to rule out correctly CAD and therefore to appropriately avoid the need of additional diagnostic methods renders CTCA an excellent tool for starting the diagnostic algorithm in patients

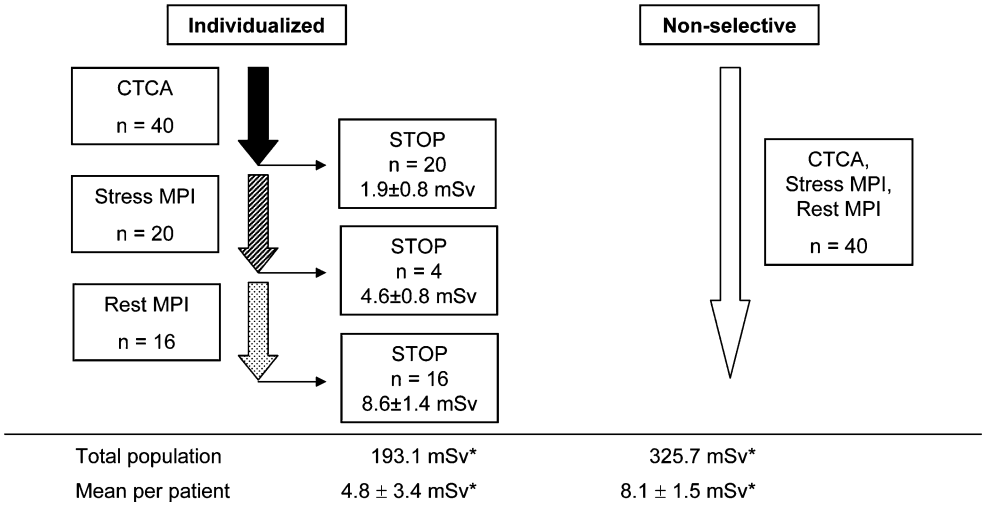

Fig. 2 Comparison of mean and total effective radiation dose for the individualized versus the non-selective algorithm (*CTCA* computed tomography coronary angiography, *MPI* myocardial perfusion imaging, *STOP* no further test required). *$p<0.001$

with low to intermediate pretest probability. By contrast, an abnormal 64-slice CTCA is a poor predictor of functionally relevant coronary stenoses [6]. Patients with positive CTCA should undergo further evaluation for obstructive CAD to ensure the physiological relevance of the lesion. Consequently, CTCA is not recommended as the first diagnostic step in patients with elevated probability of CAD or those with advanced age as the latter confers a higher prevalence of severe coronary calcifications which both severely impairs the NPV of CTCA. Thus, our findings would not necessarily hold true when extrapolated to other patient populations with higher disease prevalence for which the algorithm may need appropriate modifications.

In the present study, less than half of the patients needed all diagnostic steps, indicating that our algorithm was adequately used in the appropriate target population with low to intermediate pretest probability. As a consequence, total radiation dose to the study population was significantly reduced by about 50%, resulting in an average effective radiation dose of 4.8±3.4 mSv per patient. This represents a dose reduction in the range of a power of magnitude compared to earlier studies combining SPECT-MPI with CTCA reaching values of 41 mSv [11]. This is likely to have a major clinical impact, as the balance of harms and benefits is clearly shifted to the favorable end and therefore such combined and accurate non-invasive assessment of CAD will gain importance. This is further elucidated by the fact that almost two-thirds of all patients referred to invasive evaluation in Europe will end up with a purely diagnostic invasive CA [24]. The morbidity and mortality associated with the invasiveness of the diagnostic CA may be increasingly perceived as unjustified in view of valuable non-invasive alternatives. This is particularly true as the radiation burden of the latter was for a long time regarded as prohibitively high, but has now been massively reduced. In fact, our results document that with the latest technical refinements associated with appropriate and well-selected individualized use the resulting dose is reasonably low, comparable to half of the radiation obtained from diagnostic invasive CA.

We acknowledge the following limitations: First, this is a single-center study with only a small population of 40 patients. Therefore, the results of this hypothesizing generating pilot study may require confirmation in larger studies. Second, the present results must be read with caution when generalized to patient populations with disease prevalence different from our population. In fact, in high-prevalence populations the algorithm would need adjustments as ischemia assessment may preferably precede any structural assessment such as CTCA. Furthermore, sinus rhythm and heart rate control is required for prospective ECG-triggering [12], which explains why beta-blockers where administered frequently, although this was comparable to previous reports [12, 13]. Although some concerns have been raised on whether beta-blockade may reduce the extent and severity of SPECT-MPI, a recent systematic study has ruled out any effect of beta-blocker treatment on accuracy of SPECT-MPI [25]. Finally, although an individualized algorithm may be favorable for the individual patient, this may not be ideal for aspects of practicability, as in a busy site image reporting may not be available fast enough to allow online decisions with regard to next step scanning. Furthermore, even if such continuous decision-making would be available, it may be a challenge for many sites to implement such flexible schedules for reasons of scanner and radioligand availability.

In conclusion, this study shows that despite minimized radiation dose, the proposed low-dose stepwise rapid

algorithm accurately predicts which decision with regard to revascularization would be taken in the catheterization laboratory.

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Disclosures None

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